PREPARATION AND EVALUATION OF THE NOVEL DRUG-DRUG SOLID DISPERSION OF ATORVASTATIN CALCIUM AND LOSARTAN POTASSIUM

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

Chennai-600032

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

REG. NO: 26115406

Under the Guidance of

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This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

Signature of the Guide and Head, Department of Pharmaceutics

R. NATARAJAN, M.Pharm., (Ph.D.)

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INTRODUCTION

1. INTRODUCTION

The enhancement of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubalization by cosolvents, and particle size reduction.[1]

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability.[2] Lipophilic molecules, especially those belonging to the bio pharmaceutics classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like in complete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability.[3]

In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome. This method, which was later, termed solid dispersion which involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures.[4]

The term solid dispersion refers to a group of solid products consisting of at least two different compounds, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particle (clusters) or in crystalline particles.[5]

Solid dispersion can be prepared by various methods such as solvent evaporation and melting method. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. According to this method, a drug is thoroughly dispersed in a water-soluble carrier by suitable method of preparation. The mechanism by which the solubility and the dissolution rate of the drug are increased includes: reduction

of the particle size of drug to submicron size or to molecular size in the case where solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from amorphous to crystalline form, the high energetic state which is highly soluble; finally, the wet ability of the drug particle is improved by the hydrophilic carrier.[6]

Solid dispersion of drug helps to reduce the particle size of drug due to molecular dispersion.[7] Particle size reduction by micronization or nanonization can enhance the dissolution rate; however, the apparent solubility remains unaltered. At the molecular level, polymorphs offer a limited solubility advantage because of a small difference in free energy. In contrast, amorphous systems with excess thermodynamic properties and lower energetic barrier can offer significant solubility benefits.[8]

There were several ways in which bioavailability of the drug can be enhanced all of which aimed at increasing the surface area of the drugs which includes. Micronization, use of salt form, use of metastable polymorphs, solvent deposition, selective adsorption on insoluble carriers, solid dispersion, solute solvent complexation, complexation with cyclodextrins.[9]

Hyperlipidemia or hyperlipoprotienemia or dyslipidemia is the presence of elevated or abnormal levels of lipids or lipoproteins in the blood. Lipid and lipoprotein abnormalities are extremely common in general population and are regarded as a highly modifiable risk factor for cardiovascular diseases due to influence of cholesterol. An individual's specific biochemical and metabolic profile can often work against even the healthiest lifestyle. For these "biochemically challenged" patients, lipid-lowering agents such as the statins have literally provided a new lease on life. Atorvastatin is a selective competitive inhibitor of HMG CoA reductase. Atorvastatin reduces total cholesterol, LDL-cholesterol in patients with homozygous and heterozygous familial hypercholesteremia, non familial hypercholesteremia and mixed dyslipidemia. It also reduces the VLDL-cholesterol and triglyceride. Atorvastatin calcium is a synthetic lipid lowering agent, which competitively inhibits 3-hydroxy-3methyl-glutryl CoA.[9]

REVIEWOF LITERATURE

2. REVIEW OF LITERATURE

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption.[10]

Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation.[11]

Based upon their permeability characteristics, the biopharmaceutics classification system (BCS) classifies such drugs in two major classes, i.e., Class II and IV. The BCS class II drugs are poorly water-soluble entities with high permeability. Most formulation strategies for such drugs are targeted at enhancing their fine dispersion at absorption level.[12]

Noyesh -Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compound smight be improved to minimize the limitations to oral availability.

$$dC/dt * h = AD. (Cs - C)$$

Where, dC/dt **-** is the rate of dissolution, A **-**is the surface area available for dissolution, D **-** is the diffusion coefficient of the compound, Cs**-** is the solubility of the compound in the dissolution medium, C -is the concentration of drug in the medium at time t and h **-** is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.[13]

To increase the dissolution rate from equation the following approaches are available.

- To increases the surface area available for dissolution decreasing the particle size of drug.
- Optimizing the wetting characteristics of compound surface.
- To decrease the boundary layer thickness. Ensure sink condition for dissolution.
- Improve apparent solubility of drug under physiologically relevant conditions.
- Drug administered in fed state is a way to improve the dissolution rate.

TECHNIQUES OF SOLUBILITY ENHANCEMENT [14]

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are

Micronization:

Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug.

Nanonization:

Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nano scale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects

Nanocrystals:

The term drug nanocrystals imply a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous.

Nanosuspension:

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. Nanosuspension technology solved the problem of drugs which are poorly aqueous soluble and less bioavailability.

Nanoemulsion:

Nanoemulsions are a nonequilibrium, heterogeneous system consisting of two immiscible liquids in which one liquid is dispersed as droplets in another liquid.

Sonocrystallization:

Sonocrystallization is a novel particle engineering technique to enhance solubility and dissolution of hydrophobic drugs and to study its effect on crystal properties of drug.

Supercritical fluid method:

A supercritical fluid (SCF) can be defined as a dense noncondensablefluid is another novel nanosizing and solubilisation technology whose application has increased in recent years.

Spray freezing into liquid and lyophilization:

This technique involves atomizing an aqueous,organic, aqueous-organic cosolvent solution, aqueous organic emulsion or suspension containing a drugand pharmaceutical excipients directly into a compressed gas (i.e. carbon dioxide, helium, propane,ethane), or the cryogenic liquids (i.e. nitrogen, argon or hydrofluroethers).

Evaporative precipitation into aqueous solution:

This process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs.

Use of surfactant:

Surface active agents (surfactants) are substances which at low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy andthe surface or interfacial tension.

Use of co-solvent:

Cosolvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs. It is well-known that the addition of an organic cosolvent to water candramatically changes the solubility of drugs.

Hydrotropy method:

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. The term "*Hydrotropy*" has been used to designate the increase in aqueous solubility of various poorly watersoluble compounds due to the presence of a large amount of additives.

Use of salt forms:

A major improvement in solubility and dissolution rate can be achieved by forming a salt. Salts of acidic and basic drugs have, in general, higher solubilities than their corresponding acid or base forms.

Solvent deposition:

In this technique drug is dissolved in a solvent like methylene chloride to produce a clear solution. The carrier is then dispersed in the solution by stirring and the solvent is removed by evaporation under temperature and pressure.

Solubilizing agents:

Solubilizing materials like super disintegrants such as crospovidone,crosscarmellose sodium and sodium starch glycolate used as solubilizing agents in many formulations which increase the solubilty and dissolution rate of poorly water soluble drugs. The superdisintegrants acts as hydrophilic carrier for poorly water soluble drug.

Modification of the crystal habit:

Polymorphism is the ability of an element or compound tocrystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical,but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc.

Co-crystallisation:

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, also referred as molecular complexes.

Complexation:

The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylenen glycol, N methylglucamide. Considerable increase in solubility and dissolution of the drug has beenachieved by the use of cyclodextrins.

CLASSIFICATION OF SOLID DISPERSION:

First generation solid dispersions

First generation solid dispersions were prepared using crystalline carriers such as urea and sugar, which were the first carriers to be employed in solid dispersion. They have the disadvantage of forming crystalline solid dispersion, which were thermodynamically more stable and did not release the drug as quickly as amorphous ones.[15]

Second generation solid dispersions

Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP),polyethyleneglycols (PEG) and polymethacrylatesas well as natural product based polymers such as hydroxylpropylmethyl-cellulose (HPMC), ethylcellulose, and hydroxypropoylcellulose or starch derivates like cyclodextrins.[15]

Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self emulsifying properties. Therefore, third generation solid dispersions appeared. The use of surfactant such as inulin, inutec SP1,compritol 888 ATO, gelucire 44/14 and poloxamer407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.[15]

Significant properties of solid dispersion:

There are certain parameters that are given below when successfully controlled, can produce improvements in bioavailability[16]

1. **Particle size reduction**:

Solid dispersion represents the last state of the size reduction. It includes the principle of drug release by creating a mixture of poorly water soluble drug and highly soluble carriers, and after dissolution of carrier, the drug get molecularly dispersed in dissolution medium.

2. **Wettability:**

Carriers having surface activity like cholic acid and bile salts, when used, can significantly increase the wettability properties of drug. Recently, in third generation solid dispersion surfactants have been included that is the emerging technique.

3. **Higher porosity:**

Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate.

4. **Amorphous state of drug particles:**

Drug particles in amorphous state have higher solubility.

5. **Approaches for avoiding drug recrystallisation**

Recrystallisation is the major disadvantage of solid dispersions, as we are using amorphous drug particles and they are thermodynamically instable and have the tendency to change to a more stable state. Several polymers are being used for improving the physical stability of the amorphous drugs by increasing the Tg of the miscible mixture.

CHARACTERISATION OF SOLID DISPERSION:

Solid dispersions are characterized fir crystallanity and molecular structure in amorphous solid dispersion. Various different types of analytical methods are available to characterize solid dispersion.[17]

DETECTION OF CRYSTALLINITY IN SOLID DISPERSIONS:

Many attempts have been to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. For that purpose many techniques are available which detect the amount of crystalline material in the dispersion. The amount of crystalline material is never measured directly but is mostly derived from the amount of crystalline material in the sample. It should be noted that through the assessment of crystallinity as method to determine the amount of amorphous drug it will not be revealed whether the drug is present as amorphous drug particles or as molecularly dispersed molecule.

1. Powder x-ray diffraction (xrd)
2. Infrared Spectroscopy (ir)
3. Water Vapoursorption
4. Isothermal Microcalorimetry
5. Dissolution Calorimetry
6. Diffrential scanning Calorimetry (dsc)

Factors affecting solubility: [18]

Particle size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases.

Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased.

Pressure

For gaseous solutes, an increased in pressure increases solubility and a decreases in pressure decreases the solubility.

Nature of the solute and solvent

While only 1 gram of lead chloride can be dissolved in 100gm of water at room temperature, 200gm of zinc chloride can be dissolved.

Molecular size

Molecular size will affect the solubility. The large the molecule or the higher its molecular weight the less soluble the substance.

Polarity

Polarity of the solute and solvent molecules will affect the solubility.

Polymorphism

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant.[18]

Advantages of solid dispersion:

1. Rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and are duction in pre systemic both can lead to the need for lower doses of the drug.

2. Other advantages include transformation of the liquid form of the drug into a solid form (e.g., clofibrate and benzoyl benzoate can be incorporated into PEG 6000 to give a solid, avoidance of polymorphic changes and

There by bio-availability problems), as in the case of nabilone and PVP dispersion, and protection of certain drugs by PEGs (e.g., cardiac glycosides) against decomposition by saliva to allow buccal absorption.[16.]

DISADVANTAGES OF SOLID DISPERSIONS

The major disadvantages of SDs are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility .Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness.[19]

Limitations of solid dispersion:

The major limitation in the development of solid dispersion is the lack of suitable Manufacturing techniques that could be scaled up to commercial production. The various limitations are: [16]

- Laborious and expensive methods of preparation,
- Reproducibility of physicochemical characteristics,
- Difficulty in incorporating into formulation of dosage forms,
- scale-up of manufacturing process, and Stability of the drug and vehicle

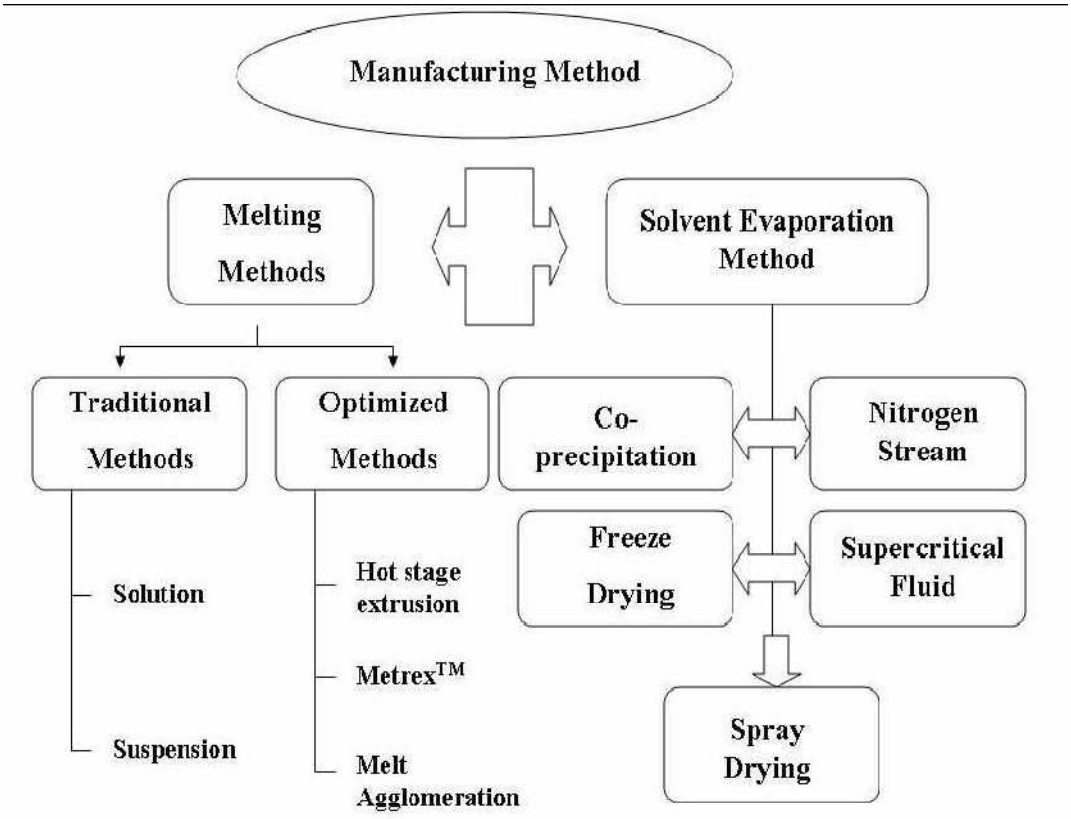
APPLICATIONS OF SOLID DISPERSION

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
- To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.
- To reduce side effect of certain drugs.
- Masking of unpleasant taste and smell of drugs.
- Improvement of drug release from ointment creams and gels.
- To avoid undesirable incompatibilities.[20,21]

Tabel.1 **Classification of Carriers Enhancing Dissolution of Drugs[18]**

S.NO	**Chemical Class**	**Examples**
1	Acids	Citric acid, Tartaric acid, Succinic acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, Cyclodextrins, Galactomannan
4	Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamine E TPGS NF
5	Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthines

Fig.1 **Methods of Preparation of Solid Dispersion**



Fusion Method

The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. However many substances, either drugs or carriers, may decompose or evaporates during the fusion process which employs high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.[20]

Advantages

- The main advantage of direct melting method is its simplicity and economy.
- In addition melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier.[20]

Disadvantages

- Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature
- A problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. It was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions.
- Degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose a temperature of 169°C was required and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. Poly ethylene glycols melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.[22]

Work done so far to improve the solubility of atorvastatin calcium

1. Preparation, characterization and In-vitro evaluation of atorvastatin calcium solid dispersions with various hydrophilic polymers and its FDT formulation. (Bhumikasharma et al., 2012)[23].

2. Enhancement of dissolution for improving bioavailability of poorly water soluble drug through oral mucosa (Tapan K. pal et al., 2012)[24].

3. Formulation and evaluation of solid dispersion of Atorvastatin with various carriers (K.R.Bobe et al., 2011)[25].

4. Enhancement of dissolution rate of atorvastatin calcium using solid dispersions by dropping method. (Lakshmi narasaiah et al., 2011)[26].

5. Water solubility enhancement of atorvastatin by solid dispersion method (Riazuddin et al., 2010)[27].

6. Formulation and characterization of atorvastatin calcium liquid solid compacts. (Sanjeev raghavendra gubbi et al., 2010)[28].

7. Improved dissolution rate of atorvastatin calcium using solid dispersions with PEG-4000(Kalyan reddy .B et al., 2010)[29].

8. Enhancement of dissolution for improving bioavailability of poorly water soluble drug through oral mucosa (Tapan K. pal et al., 2012)[30].

9. A novel drug-drug solid dispersion of hydrochlorothiazide-losartan potassium (N.N Rajendran., et al 2010)[31].

10. In vitro availability of atorvastatin in presence of losartan (safed arayne M.et al.,2006)[32].

AIM AND OBJECTIVE

3. AIM AND OBJECTIVE

AIM:

To Prepare and evaluate the novel drug – drug solid dispersion of Atorvastatin calcium – Losartan potassium and to improve the solubility of atorvastatin calcium by fusion method.

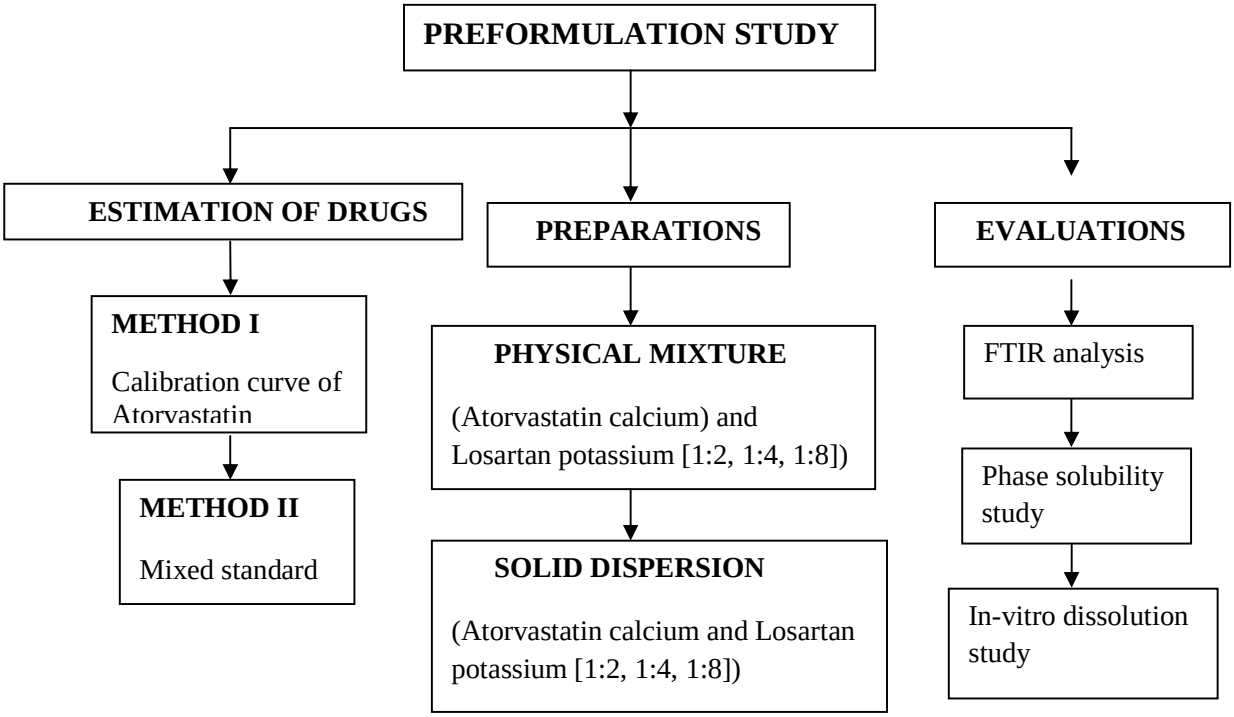
OBJECTIVE

To estimate the following parameters.

- FTIR analysis of pure drugs, physical mixtures and solid dispersions.
- Calibration curve of atorvastatin calcium.
- Calibration curve of losartan potassium.
- Preparation of physical mixtures (1:2, 1:4, 1:8 ratios).
- Preparation of solid dispersions (1:2, 1:4, 1:8 ratios).
- Phase solubility study of Atorvastatin calcium - Losartan potassium**.**
- In-vitro dissolution of pure drugs, physical mixtures and solid dispersions.
- Release kinetic study.

PLAN OF WORK

4. PLAN OF WORK



PROFILES

5. PROFILES

DRUG PROFILE

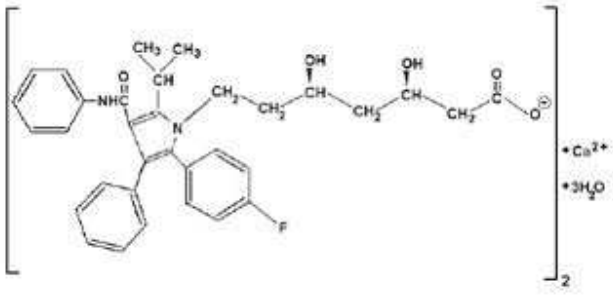
Atorvastatin calcium[32]

Category **:** Antihyperlipidermic agent

Empirical formula **: C**$_{66}$ H$_{68}$ CaF$_2$N$_4$0$_{10}$.3H$_2$o

Molecular weight **:** 1209.42

Chemical structure **:**



Solubility **:** Very slightly soluble in water, slightly soluble in Ethanol, freely soluble in methanol

Chemical name **:** Calcium -2-(p-fluorophenyl)-beta, delta-dihydroxy-5-Isopropyl-3-phenyl-4-(phenylcarbamoly) pyrrole-1-heptan oic acid (1:2)trihydrate.

Functional category : HMG-CoA reductase inhibitors.

Pharmacology

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the ratelimiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

Pharmacokinetics

Absorption:

Atorvastatin is rapidly absorbed after oral administration; maximum plasmaconcentrations occur within 1 to 2 hours. Extent of absorption increases in proportion toatorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) isapproximately 14% and the systemic availability of HMG-CoA reductase inhibitoryactivity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%,respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution:

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

Metabolism

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme.

Excretion

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo 3enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Duration

The haff curve of HMG-CoA reductase inhibition is 20 to 30 hours.

Contraindications

Active liver disease or unexplained persistent elevation of serum transaminases; pregnancy;lact.

Dosage and Administration

Adults

10 to 80 mg/day.

Pharmacodynamics

Adverse Reactions

CNS **:** Headache, Asthena, dizziness, insomnia.

ENT **:** Sinusitis, Pharyangitis, Rhinitis.

Dermatologic **:** Rash, Stevens-johnson syndrome, bullous rashes including erythema multiforme Toxic epidermal necrolysis

GI **:** Sinusists,abdominal pain, constipation, dyspepsia, Nausea.

Genitourinary : Albuminuria, Hematuria.

Metabolic : Peripheral edema (at least 2%)

Musculoskeletal **:** Myalgia, Arthralgia, Arthritis, Rhabdomyolysis.

Respiratory **:** Bronchitis

Miscellaneous **:** Accidental injury, flu-like symptoms, chest pain, Angioneurotic edema.

Drug Interaction

Co administration of Antacids, Cholestrol, rifampin may decrease atorvastatin level.Azole antifungal agent (eg,itraconazole), cyclosporine, diltiazem, gemfibrozil, grapefruit juice, macrolide antibiotics (eg,erythromycin), niacin,NNRTIs, protease inhibitors (eg,ritonavir), verapamil, severe myopathy or rahabdomyolysis may occur.

LOSARTAN POTASSIUM[33]

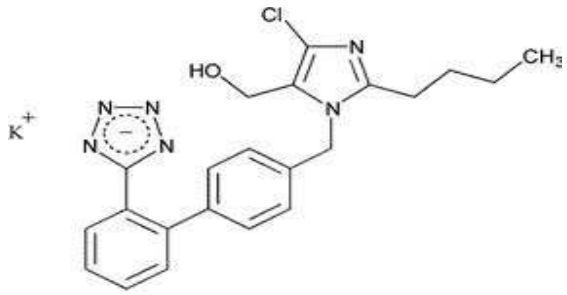
Category : Antihypertensive

Empirical formula : $C_{22}H_{22}C_lKN_6O$

Molecular weight : 461.01

Solubility : freely soluble in water, soluble in alcohols, and slightly Soluble in organic solvents, such as acetonitrile and methyl ethyl ketone.

Chemical structure :



Chemical name : 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-

yl]methyl]-1*H*-imidazole-5-methanol monopotassium salt.

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT2receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active

metabolite do not exhibit any partial agonist activity at the AT1 receptor and have much greater affinity (about 1000-fold) for the AT1 receptor than for the AT2 receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT1 receptor. Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics

Following oral administration, losartan is well absorbed and undergoes substantial first-passs metabolism. The systemic bioavailability of losartan is approximately 33%, About 14% of an orally administered dose of losartan is converted to the active metabolite. Mean peak plasma concentrations of losartan and its active metabolite are reached in 1 hour and 3-4hours respectively. While maximum plasma concentrations of Losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of Losartan. A meal slows absorption of losartan and decreases its Cmax-but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decrease). Both Losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Studies in rats indicate that Losartan crosses the blood-brain barrier poorly, if at all about 4% of the dose is excreted unchanged in urine and about 6% is excreted unchanged in urine as active metabolite. Biliary excretion contributes to the elimination of Losartan and its metabolites. Losartan pharmacokinetics have not beeninvestigated in patients <18 years of agem Losartan pharmacokinetics have been investigated in the elderly(65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan are about twice as high in female hypertensives as in male hypertensives. But concentrations of the active metabolite are similar in males and females. No dosage adjustment is necessary.

INDICATIONS

Losartan potassium is indicated for the treatment of mild to moderate hypertension. It may be used alone or in combination with other antihypertensive agents.

Dosage and Administration

Hypertension

Adult's Initial dose

PO 50 mg/day; 25 mg/day if volume depleted or history of hepatic impairment.

Maintenance dose

PO 25 to 100 mg/day.

Children 6 yr of age and older Initial dose

PO 0.7 mg/kg (max, 50 mg) once daily.

Maintenance dose

PO 0.7 to 1.4 mg/kg/day (max, 100 mg).

Nephropathy in Type 2 Diabetes Adults Initial dose

PO 50 mg/day; the dose may be increased to 100 mg/day based on BP response

Drug Interactions:

Losartan may increase levels of blood potassium (hyperkalemia), which can lead to serious heart problems (arrhythmias). Therefore, concomitant use of other drugs or substances that increase blood-such as potassium-sparing diuretics (for example, spironolactone [Aldactone], triamterene, and amiloride), potassium supplements, or salt substitutes containing potassium may lead to dangerous increases in serum potassium.Combining losartan or other ARBs with non steroidal anti-inflammatory drugs (NSAIDs) in patients who are elderly, fluid-depleted (including those on diuretic

therapy), or with poor kidney function may result in reduced kidney function, including kidney failure. These effects usually are reversible. The antihypertensive effect of losartan may be reduced by aspirin and other NSAIDs such as ibuprofen (Advil, Children's Advil/Motrin, Medipren, Motrin, Nuprin, PediaCare Fever, etc.), indomethacin (Indocin, Indocin-SR), and naproxen (Anaprox, Naprelan, Naprosyn, Aleve).

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the in vitro alkaline elution and in vitro and in vivo chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, in vitro alkaline elution, and in vitro chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p<0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In non pregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg)

Contraindications

Losartan potassium is contraindicated in patients who are hypersensitive to any component of this product

MATERIALS

6. MATERIALS AND METHODS

ACTIVE INGREDIENTS USED:

Table 2: Ingredients used for the experiment

S. No	Name of the ingredient	Manufacturer/Suppliers
1.	Atorvastatin calcium	Dr.Reddy'S Laboratories,Ltd.
2.	Losartan potassium USP	Medrich Pvt. Ltd.

INSTRUMENTS USED:

Table 3: Instruments used for the experiment

S. No	Name of the instrument	Manufacturing company
1.	UV – Spectrophotometer	Perkin Elmer
2.	FTIR-Spectrophotometer	Perkin Elmer spectrum RX1 FT-IR
3.	Weighing Balance	Schimadzu
4.	USP Programmable Dissolution Apparatus	Veego

METHODOLOGY

7. METHODOLOGY

ESTIMATION OF PURE DRUGS, PHYSICAL MIXTURES AND SOLID DISPERSIONS

Preparation of Standard Solutions

Standard solution of 100mg each of Losartan potassium and atorvastatin calcium were carried out using phosphate buffer (pH 6.8).

Mixed Standard

This method was adapted to pure Atorvastatin and losartan potassium.100mg was accurately weighed and dissolved in phosphate buffer (pH 6.8). Further, dilutions were made to get 1, 2, 3, 4 & 5µg/ml the sample points 236nm for Losartan potassium and 248nm for atorvastatin calcium. A standard curve was constructed by plotting the absorbance vs. concentration of the drug taken.

Preparation of PH 6.8 phosphate buffer

Placed 50 ml of 0.2 M Potassium dihydrogen phosphate in a 200 ml volumetric flask, added specified volume of 22.4 ml of 0.2 M NaOH and then added water to make the volume.

0.2 M Potassium dihydrogen phosphate

Dissolve 27.218 gm of potassium dihydrogen phosphate in distilled water and dilute to 1000 ml with distilled water.

0.2 M NaOH solution

Dissolved 8 gm of NaOH in distilled water and diluted to 1000 ml with distilled water.

PREPARATION OF PHYSICAL MIXTURE AND SOLID DISPERSION:

Preparation of physical mixture

Atorvastatin calcium and Losartan potassium were accurately weighed at the ratio of 1:2, 1:4; 1:8 (10: 20mg, 10: 40mg, 10: 80mg) pulverized, and then mixed thoroughly in a glass mortar with pestle until it becomes homogenous. The mixtures were passed through a 250µm sieve for further evaluation.

Preparation of solid dispersion

Solid dispersion of Atorvastatin calcium and Losartan potassium at three ratios of 1:2, 1:4, 1:8 (10:20mg, 10:20mg, 10:80mg) was prepared by fusion method. Atorvastatin calcium and Losartan potassium was heated it directly until it is melted. The melted mixture was then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass was crushed and pulverized. After dried solid dispersion was passed through a 250µm sieve. Sample was stored in a desiccators and used for further investigation.

Table.4 **Formulation of physical mixtures and solid dispersions of Atorvastatin calcium - Losartan potassium**

S.NO	Physical mixture (AVT:LSP)		Solid dispersion (AVT:LSP)	
1.	1:2	F1PM	1:2	F1SD
2.	1:4	F2PM	1:4	F2SD
3.	1:8	F3PM	1:8	F3SD

Evaluation of formulations

The prepared formulations of solid dispersion and physical mixture were evaluated for the following

a. Physico-chemical characterization.
b. In vitro dissolution studies

PHYSICO CHEMICAL CHARACTERIZATION:

Compatibility study

Fourier transform infrared spectroscopy was employed to characterize the possible interactions between the Atorvastatin calcium and Losartan potassium. In this study pure drug, physical mixture, solid dispersions were studied by FTIR spectrophotometer.

Estimation of Drug Content AVT

For drug content uniformity test, The powder equivalent to 10 mg of AVT was dissolved in about 10 ml of methanol an transferred into 100 ml of volumetric flask and volume was made up using phosphate buffer (pH 6.8) and the solution was filtered using (Whatmann No. 1 filter paper). The AVT content in the filtrate was determined by measuring the absorbance at 248 nm using UV spectrophotometer after appropriate dilution with phosphate buffer (pH 6.8). The drug content was determined using the standard calibration curve.

Estimation of Drug Content LSP

For drug content uniformity test, The powder equivalent to 10 mg of LSP was dissolved in about 10 ml of methanol an transferred into 100 ml of volumetric flask and volume was made up using phosphate buffer (pH 6.8) and the solution was filtered using (Whatmann No. 1 filter paper). The AVT content in the filtrate was determined by measuring the absorbance at 248 nm using UV spectrophotometer after appropriate dilution with

phosphate buffer (pH 6.8). The drug content was determined using the standard calibration curve.

Determination of phase solubility of Atorvastatin calcium/ Losartan potassium

Drug solubility studies were performed in triplicate by adding excess amount of ATV to distilled water and buffer solutions having different pH (6.8). Solutions containing flasks were kept on a Rotary Shaking Incubator for 24 hrs. After 24 hrs, solutions were analysed using UV spectrophotometer.

In vitro Dissolution study

In vitro dissolution studies of the pure drug (AVT), the selected ratios of solid dispersions and physical mixtures (equivalent to 10mg ATV filled in hard gelatin capsules using stainless steel sinkers) were performed using USP type II (Paddle) apparatus with paddle rotating at 75 rpm in 900ml of phosphate buffer pH 6.8 at 37 ± 0.5ºC. At fixed time intervals, 5ml samples were withdrawn, filtered and replaced with phosphate buffer pH 6.8. Concentration of AVT in each sample was determined by UV spectrophotometer.

KINETIC ANALYSIS OF *IN VITRO* RELEASE RATES OF FORMULATIONS

The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero-order kinetic model-cumulative percentage drug release versus time.
2. First- order kinetic model-log cumulative percentage drug release remaining versus time.

1. Zero-order kinetics

Zero order release would be predicted by the following equation:-

$$A_t = A_0 - K_0 t$$

Where,

A_t = Drug release at time 't'

A_0 = Initial drug concentration

K_0 = Zero order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

2. First- order kinetics

First-order release would be predicted by the following equation:-

$\text{Log } C = \log C_0 - K_t / 2.303$

Where,

C=Amount of drug remained at time t

C_0=Initial amount of drug

K=First-order rate constant (hr^{-1})

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant K can be obtained by multiplying 2.303 with slope values.

RESULTS

8. RESULTS

Table. 5 Calibration data of Atorvastatin calcium

S.NO.	Concentration of atorvastatin calcium(µg/ml)	Absorbance at 248nm
0	0	0
1	1	0.0625
2	2	0.1142
3	3	0.1856
4	4	0.2452
5	5	0.3107

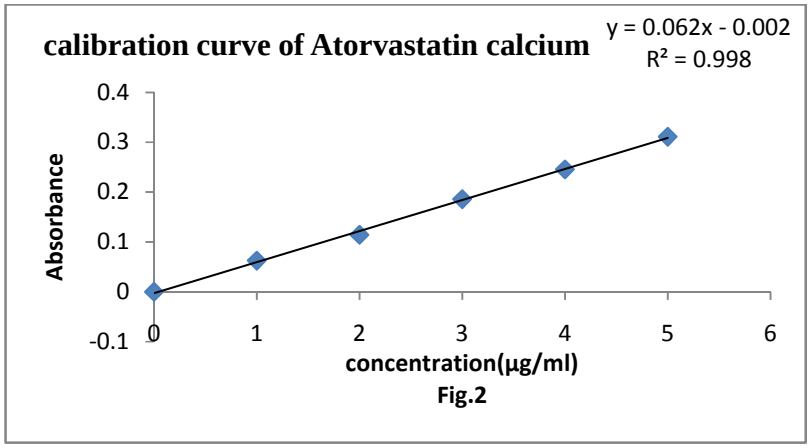


Fig.2

Table. 6 Calibration data of Losartan potassium

S.NO	Concentration of Losartan potassium(µg/ml)	Absorbance at 236nm
0	0	0
1	1	0.0656
2	2	0.1290
3	3	0.1825
4	4	0.2482
5	5	0.3166

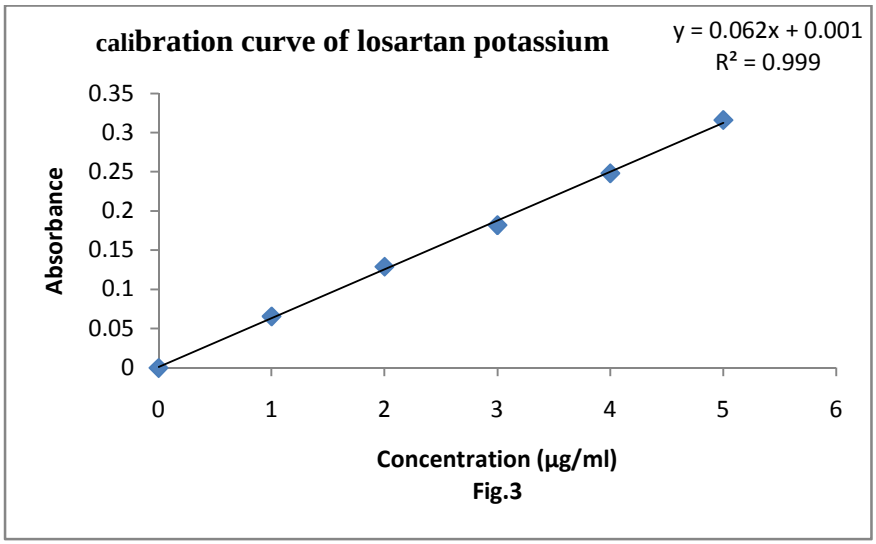


Fig.3

Compatibility study (Fourier transform infrared spectroscopic studies)

Fourier transform infrared spectroscopy was employed to characterize the possible interactions between the Atorvastatin calcium and Losartan potassium. In this study pure drug, physical mixture, solid dispersions were studied by FTIR spectrophotometer

Fig.4 **FTIR SPECTRA OF PURE ATORVASTATIN CALCIUM**

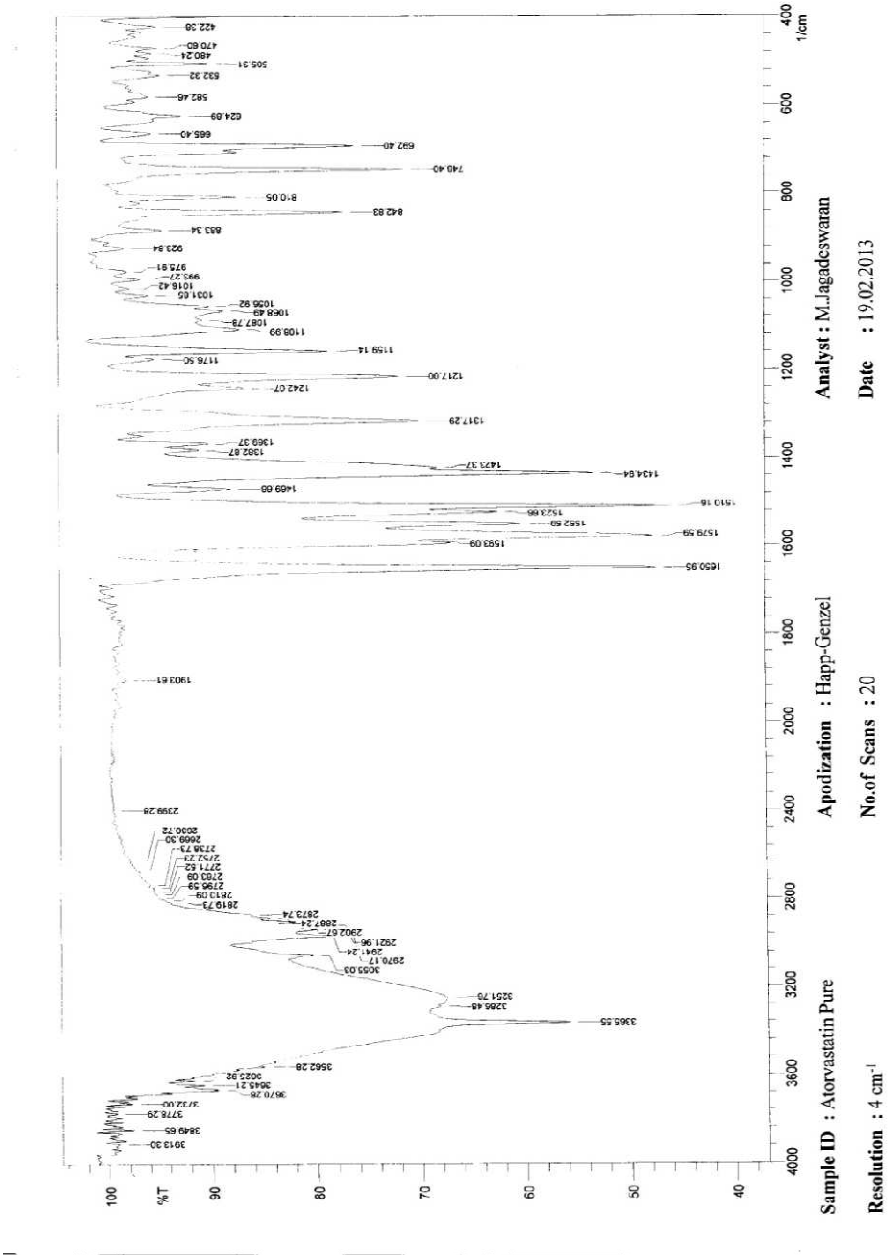


Fig.5 **FTIR SPECTRA OF PURE LOSARTAN POTASSIUM**

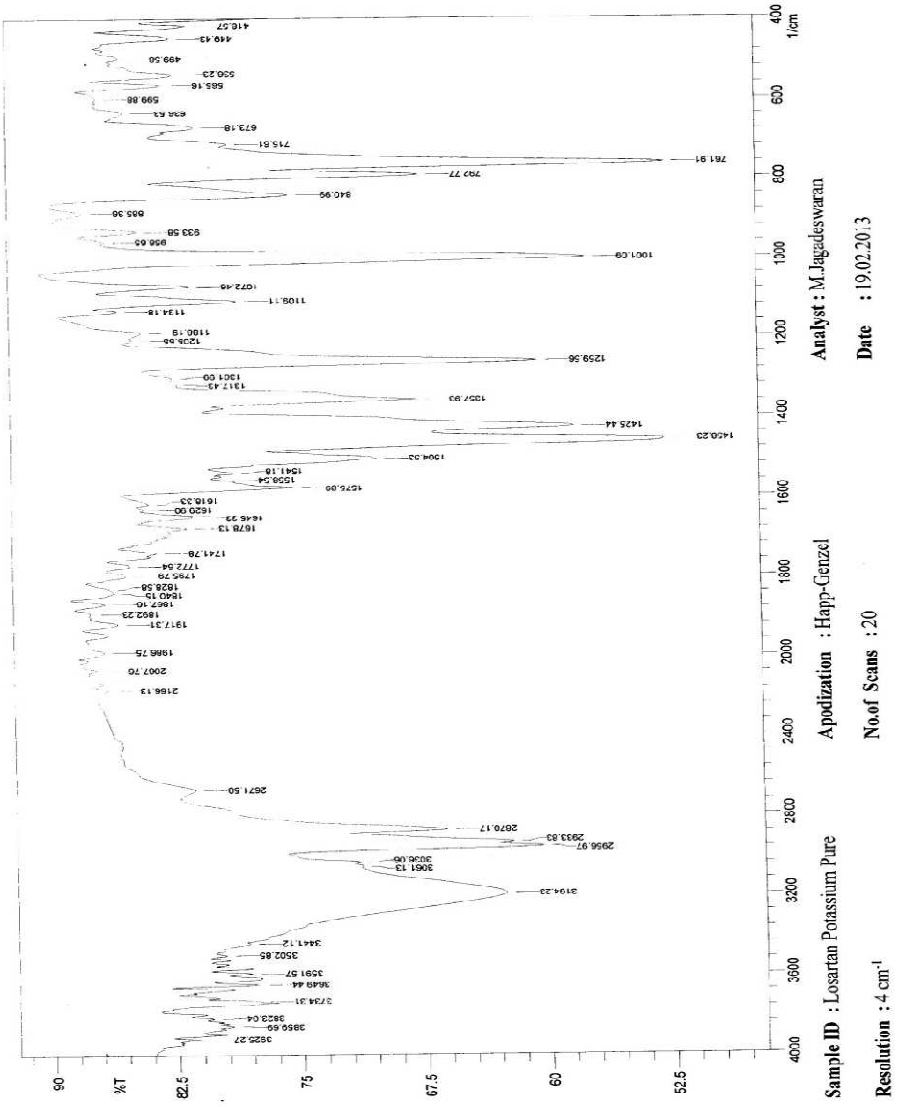


Fig.6 **FTIR SPECTRA OF AVT AND LSP (F2PM) (1:4)**

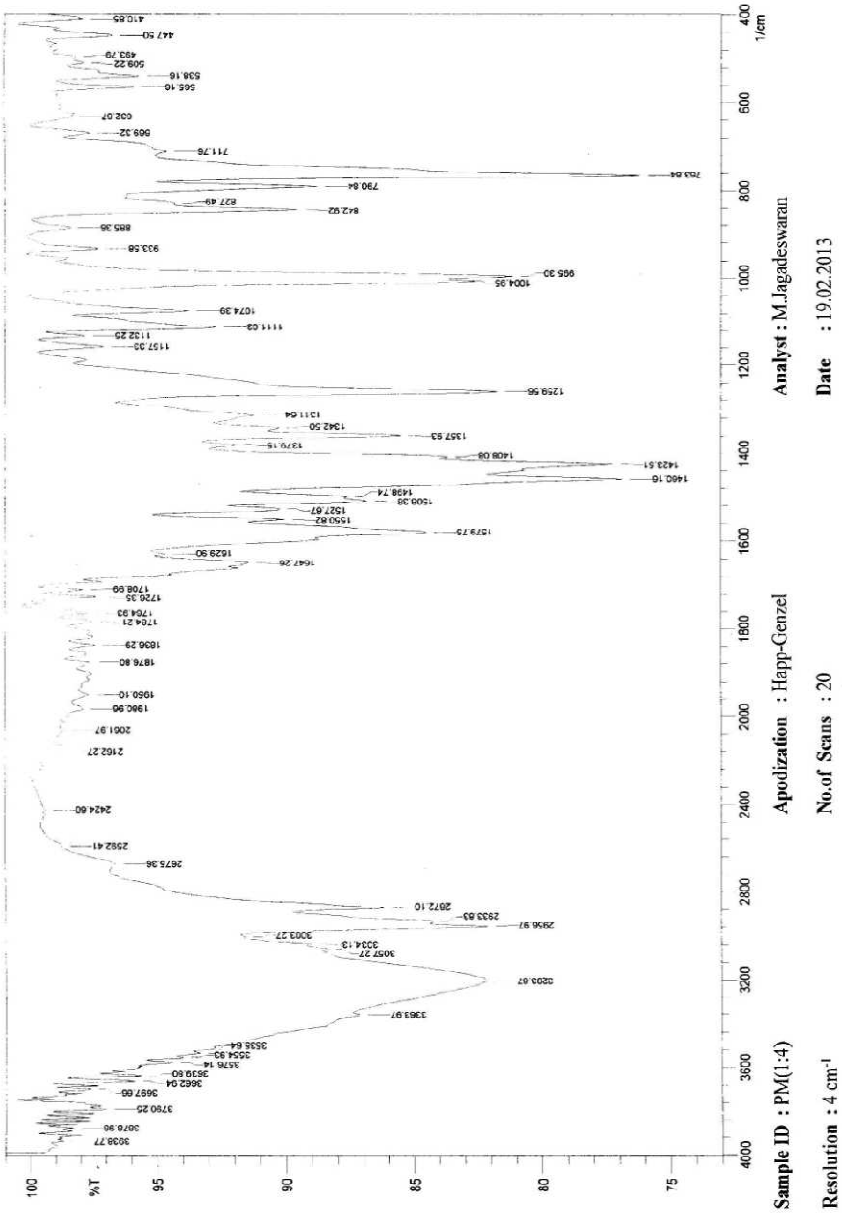


Fig.7 **FTIR SPECTRA OF HCT AND LSP (F3PM) (1:8)**

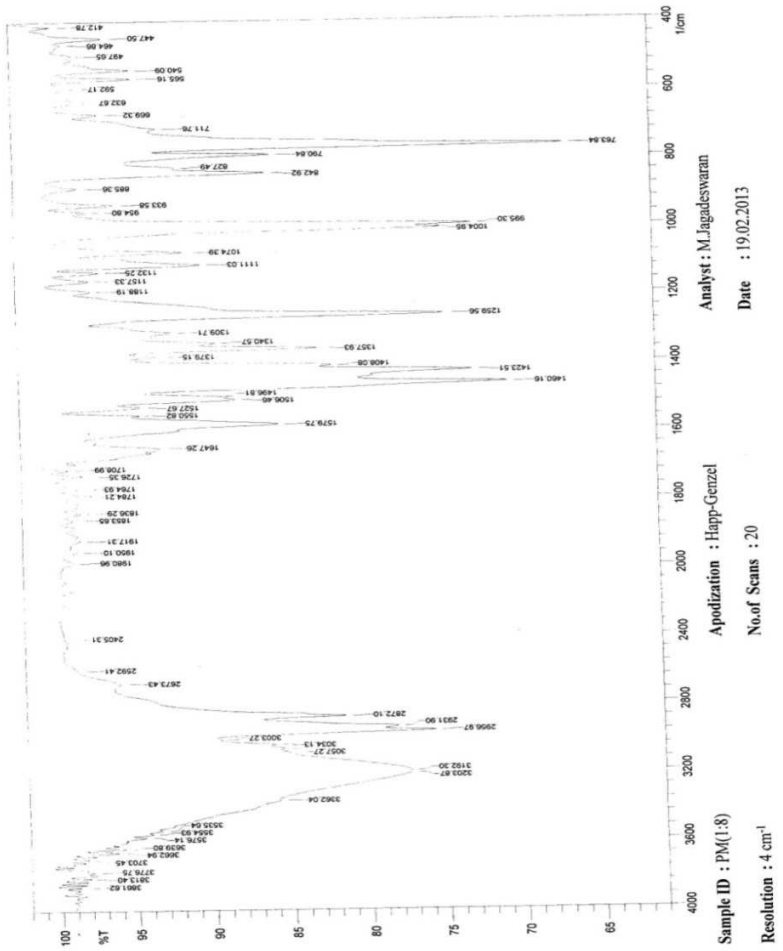


Fig.8 FTIR SPECTRA OF HCT AND LSP (F2SD) (1:4)

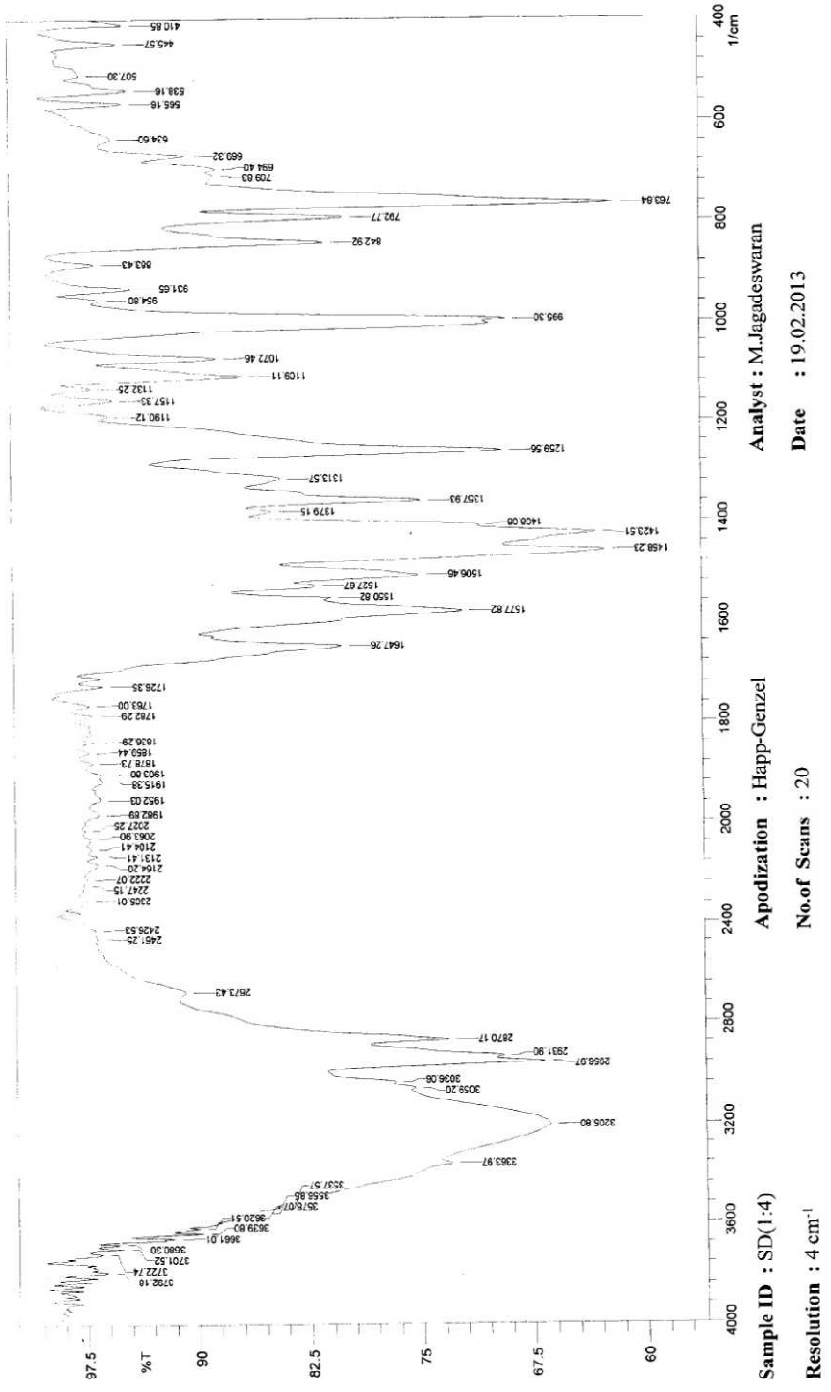
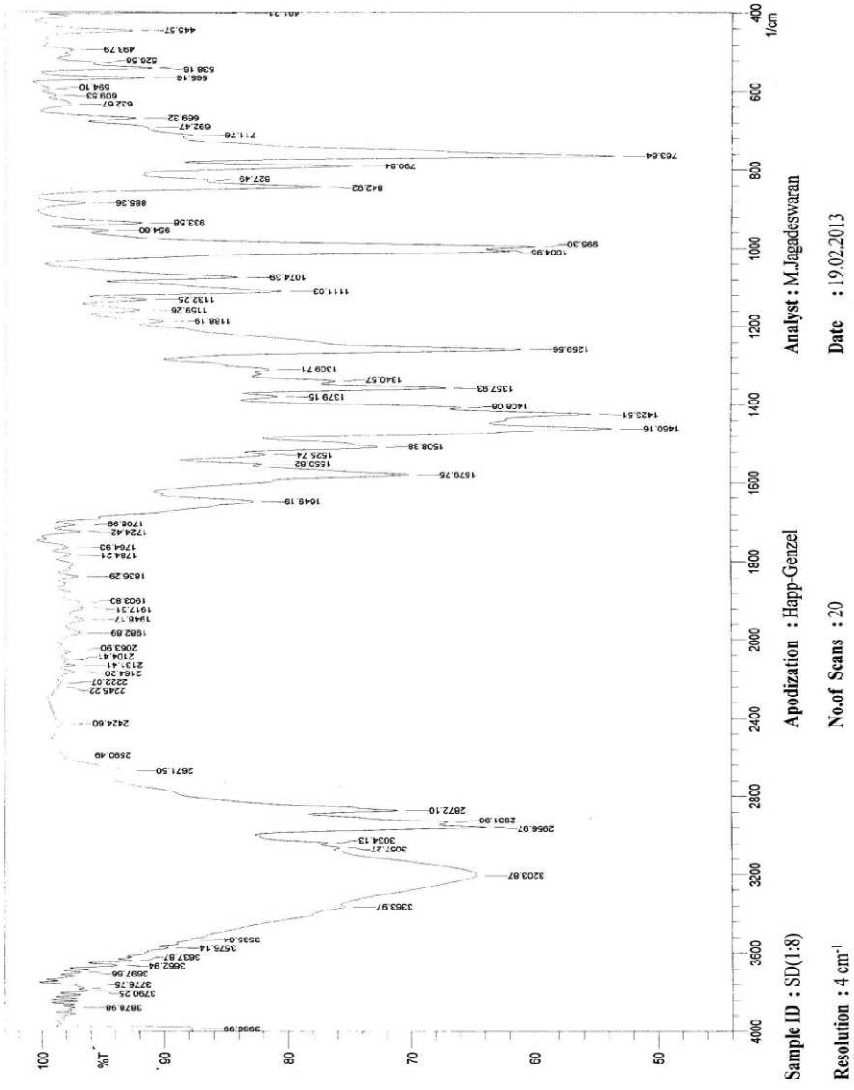


Fig.9 **FTIR SPECTRA OF HCT AND LSP (F3SD) (1:8)**



ESTIMATION OF DRUG CONTENT

Both methods I and II produced linearity in the graph obtained by plotting concentration versus absorbance. There was no interference in the analysis of drugs.

Table. 7 Calibration curve data for Atorvastatin calcium-Losartan Potassium absorbance in combination

S.No	Concentration 0f drug (µg/mL)	Absorbance of Atorvastatin calcium At 248nm	Absorbance of Losartan potassium at 236nm
1	10	0.02	0.03
2	20	0.73	0.82
3	30	1.44	1.72
4	40	2.19	2.58
5	50	2.78	3.25
6	60	3.57	4.01

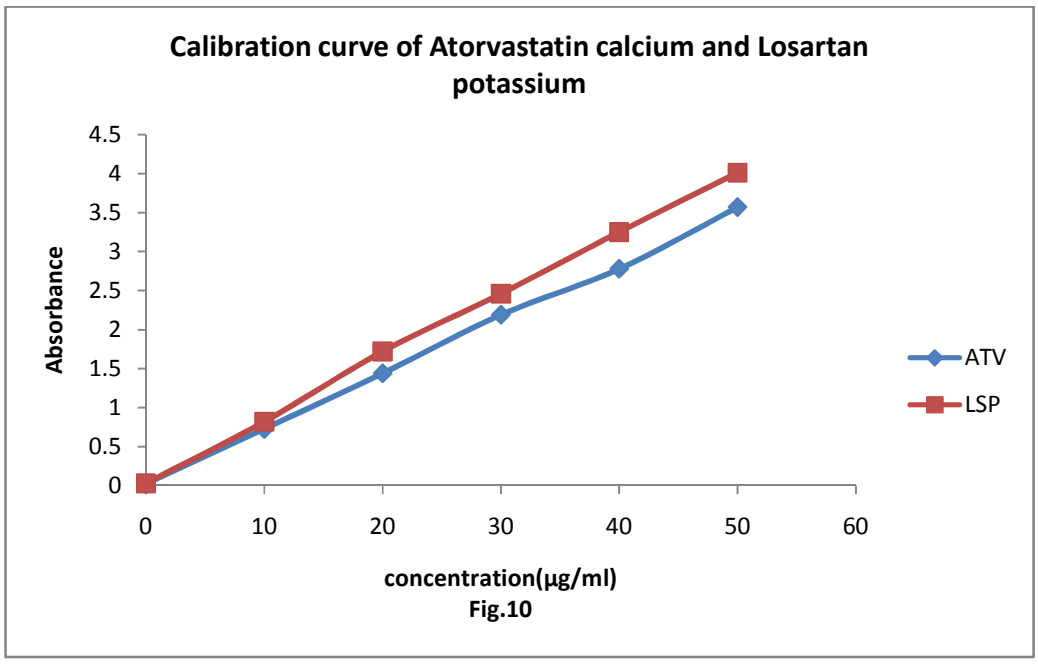


Fig.10

PHASE SOLUBILITY STUDY

Phase solubility study was carried out in order to ascertain the effect of LSP on the solubility characteristics of AVT. The results are presented in Table -8 and Figure -11. Solubility of AVT was increased as the concentration of LSP increased. The solubility of AVT was minimal in PH 6.8 and increased approximately eight fold at 0.01% w/v of LSP in 6.8buffer. These data indicates that LSP in PH 6.8 acted as a new vehicle and solubility of AVT was greatly enhanced, possibly due to the solvent effect of LSP.

Table. 8

S.No	Concentration of Losartan Potassium (%w/v)	Solubility of Atorvastatin calcium in Losartan potassium solution (mg/ml)
1	0	0.2123
2	0.0025	0.3610
3	0.0050	0.5270
4	0.010	0.010

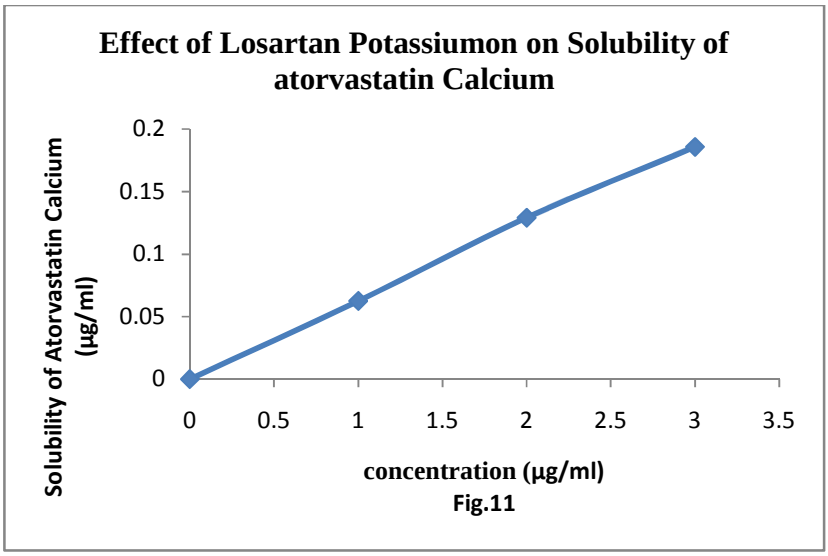


Fig.11

In-vitro dissolution studies

The data of the In vitro dissolution studies as cumulative % drug release Vs time performed on PMs and SDs on PH 6.8 buffer there were differences in dissolution pattern of AVT between F1PM, F2PM and F3PM formulations. The % drug dissolved at every time point intervals was statistically analyzed and it was observed at 10 min. The % drug dissolved from PMs was found to increase as the concentration of LSP is increased and all the PMs showed about 90% release of AVT in 80min. When compared with pure AVT PMs showed faster dissolution while pure AVT dissolved 59% at 90 min the PM dissolved 90% AVT in 80min.Thus showing faster dissolution of AVT from PMs as compared to pure AVT. Though there was a significant difference in dissolution pattern of AVT from PMs at different time intervals, no significant difference was observed in dissolution pattern all PMs at 80 min, at which fine point 90% dissolution of AVT was observed. Since LSP is freely soluble in dissolution media a uniform dissolution pattern of this drug was observed from PMs. SDs showed similar dissolution pattern as observed with PMs at different time point intervals and there were significant differences in percent (AVT) drug dissolved between different time point intervals. However SDs showed faster dissolution of AVT as compared to PMs. 90% dissolution of AVT was at shorter time (50min) from F3SD formulation as compared to F1SD, F2SD formulations which showed 90% dissolution of AVT at longer time (70min). These finding suggests that SDs showed faster dissolution rate of AVT as compared to PM or pure drug. The enhanced dissolution of AVT from PMs is due to the solvent effect of LSP. The magnitude of dissolution was significantly higher from SDs as compared to PMs the mechanisms for improved dissolution of AVT from SD is due to firstly, the solvent effect of LSP on the solubility of AVT; Secondly the change of physical state of AVT from crystallinity to amorphous state and thirdly possible micronization of poorly soluble AVT, reduced particle size, larger surface area and so enhanced dissolution of the drug in the environment. The dissolution pattern of LSP whether from PM or from SD assumes no significance in the study as the drug is freely soluble.

Table. 9 **In-Vitro Dissolution Profile of Pure Atorvastatin calcium**

Time(min)	Trail 1	Trail 2	Trail 3	Mean cumulative %drug release
0	0	0	0	0
10	3.04	3.42	3.86	0.344±0.410
20	8.90	9.20	9.28	9.12±0.200
30	14.36	13.86	14.33	14.18±0.280
40	19.17	19.83	18.94	19.31±0.462
50	25.60	25.47	26.26	25.77±0.423
60	33.82	34.44	33.59	33.95±0.439
70	44.93	44.46	45.21	44.86±0.379
80	53.26	52.71	52.89	52.95±0.280
90	58.63	58.82	60.06	59.17±0.776

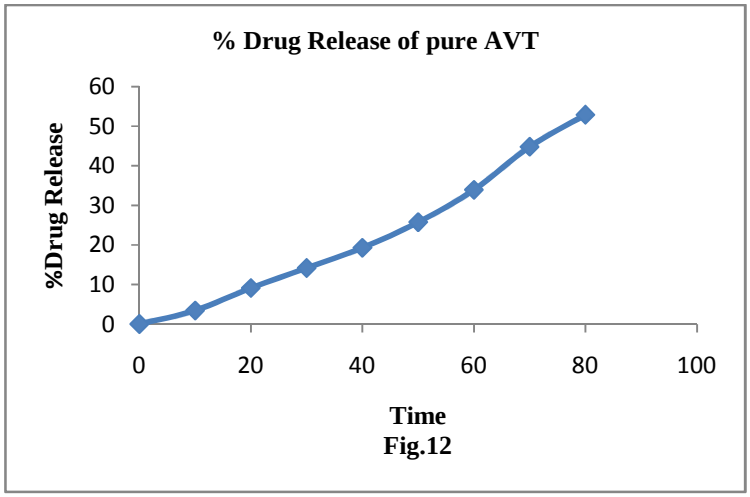


Fig.12

Table. 10 **In-Vitro Dissolution Profile of Pure Lossartan potassium**

Time(min)	**Trail 1**	**Trail 2**	**Trail 3**	**Mean cumulative %drug release**
0	0	0	0	0
10	78.14	77.36	78.94	78.14±0.210
20	79.77	80.08	80.29	82.04±0.261
30	83.78	84.26	84.41	84.15±0.329
40	87.15	86.92	87.33	87.13±0.205
50	90.42	89.34	89.75	89.17±0.365
60	91.92	92.45	92.28	92.21±0.270
70	94.55	93.94	94.40	94.29±0.317
80	95.05	95.68	95.20	96.31±0.329
90	97.85	97.26	97.42	98.17±0.294

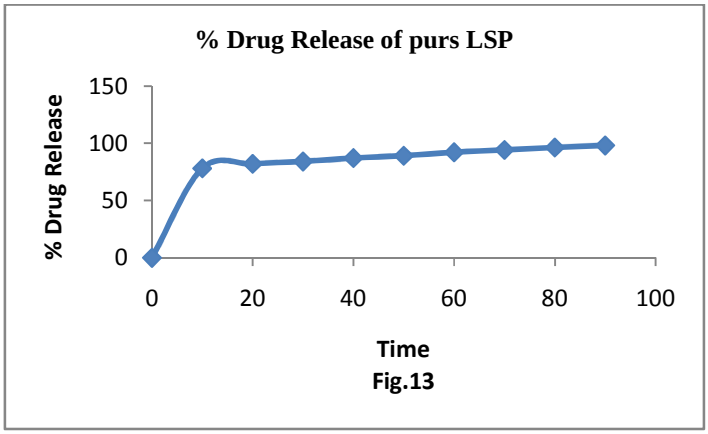


Fig.13

Table. 11 **In-vitro Dissolution Profile for F1PM**

Atorvastatin calcium					**Losartan Potassium**			
Time (min)	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**
0	0	0	0	0	0	0	0	0
10	21.08	20.63	21.46	21.05±0.415	79.61	80.03	80.17	79.93±0.291
20	40.77	41.31	41.28	41.12±0.303	81.92	83.06	82.12	82.36±0.608
30	60.67	61.42	61.06	61.05±0.375	84.26	83.76	84.36	84.12±0.321
40	68.94	69.44	68.65	69.01±0.399	86.20	86.34	85.82	86.12±0.269
50	74.81	75.22	75.39	75.14±0.296	88.92	90.06	89.66	89.54±0.578
60	80.46	80.32	79.60	80.12±0.461	90.30	91.77	91.81	91.293±0.860
70	87.30	86.88	87.74	87.30±0.430	91.20	92.14	92.27	91.87±0.583
80	90.77	91.09	91.38	91.08±0.305	94.39	93.71	94.40	94.16±0.395
90	94.20	94.73	93.86	94.26±0.438	95.88	96.16	95.71	95.91±0.887

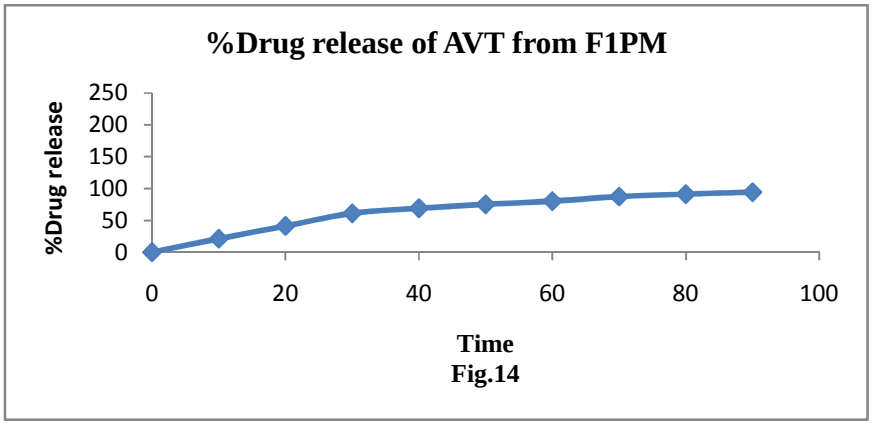


Fig.14

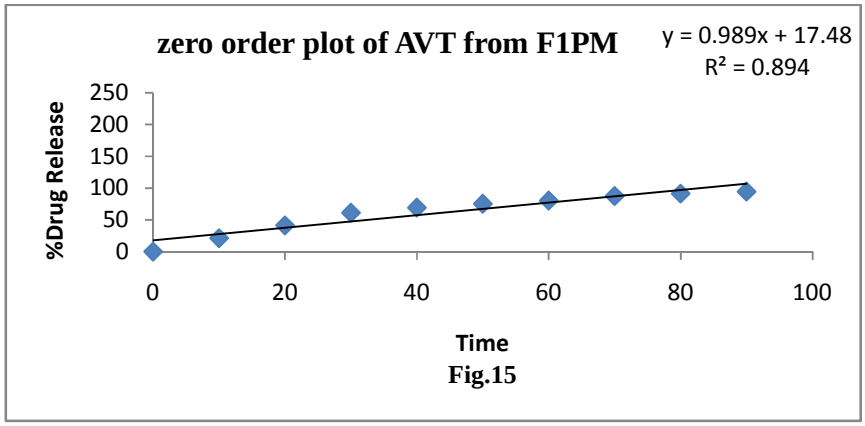


Fig.15

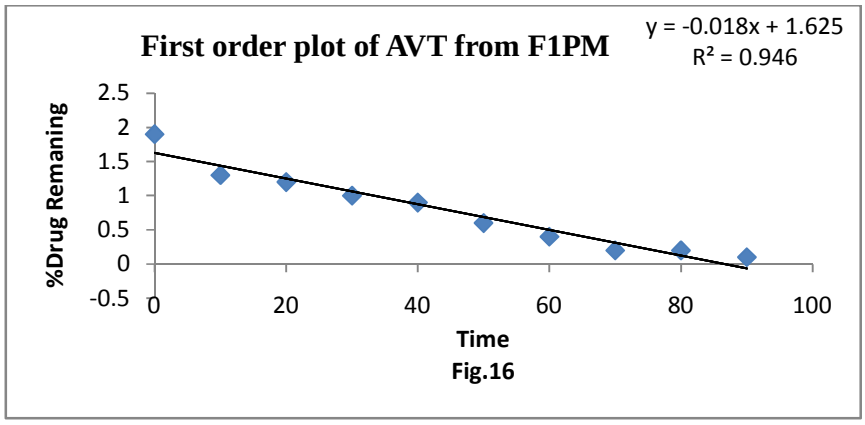


Fig.16

Table. 12 **In-vitro Dissolution Profile for F2PM**

Atorvastatin calcium					**Losartan Potassium**			
Time (min)	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**
0	0	0	0	0	0	0	0	0
10	18.21	19.80	18.46	18.82±0.855	79.51	78.87	79.25	79.21±0.321
20	36.27	36.41	35.76	36.14±0.342	82.95	84.01	83.42	83.46±0.531
30	63.80	64.46	64.08	64.11±0.331	87.60	87.22	86.35	87.05±0.640
40	69.63	70.24	70.16	70.01±0.331	91.17	90.75	91.41	91.11±0.334
50	78.40	77.88	78.33	78.20±0.282	92.85	91.95	93.03	92.61±0.578
60	83.27	83.64	82.69	83.2±0.418	93.77	94.10	94.39	94.08±0.310
70	86.92	87.05	87.36	87.11±0.226	94.91	95.45	95.33	95.23±0.283
80	92.66	91.82	93.08	92.52±0.641	95.79	96.25	96.53	96.19±0.373
90	95.15	94.77	95.23	95.05±0.245	97.11	96.55	97.47	97.04±0.463

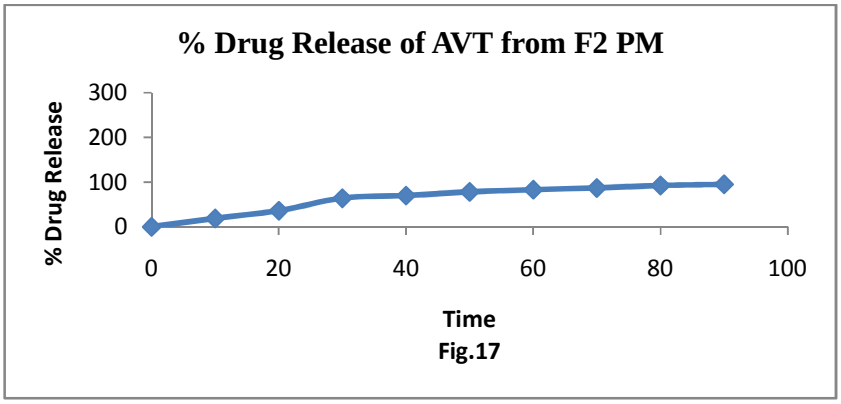


Fig.17

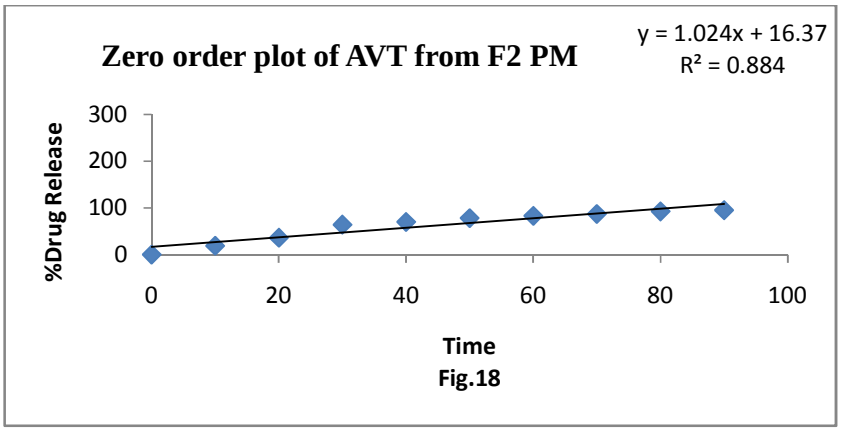


Fig.18

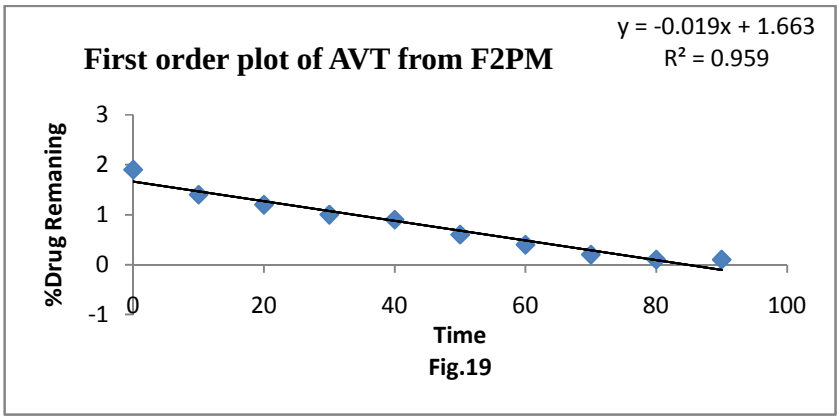


Fig.19

Table. 13 **In-vitro Dissolution Profile for F3PM**

Atorvastatin calcium					**Losartan Potassium**			
Time (min)	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**
0	0	0	0	0	0	0	0	0
10	25.75	25.86	26.16	25.92±0.212	81.15	80.75	80.86	80.92±0.206
20	44.76	45.08	45.35	45.06±0.296	85.72	86.07	85.87	85.88±0.175
30	66.15	65.88	66.27	66.01±0.199	88.77	89.16	89.34	89.09±0.291
40	71.96	73.02	72.77	72.58±0.554	92.56	93.04	92.72	92.77±0.244
50	79.65	79.53	78.92	79.36±0.391	93.66	94.18	94.41	94.08±0.384
60	83.72	82.95	84.06	83.57±0.568	96.29	95.56	95.35	95.73±0.493
70	87.81	87.63	86.55	87.33±0.681	97.35	98.02	97.23	97.53±0.425
80	92.54	92.15	91.73	92.14±0.405	98.07	97.51	97.63	97.73±0.294
90	97.31	97.16	96.68	97.05±0.329	97.83	98.48	98.55	98.28±0.397

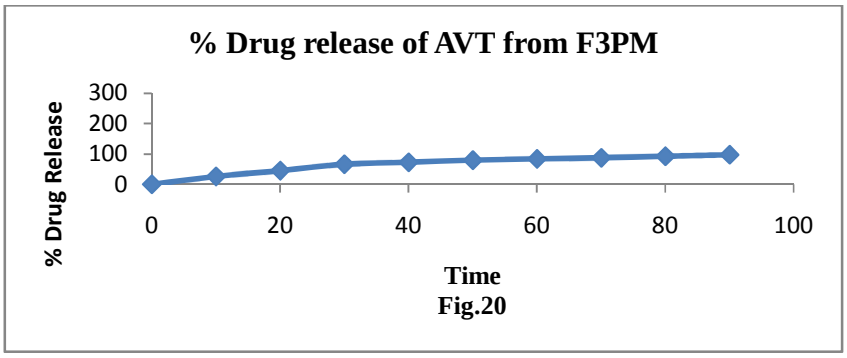


Fig.20

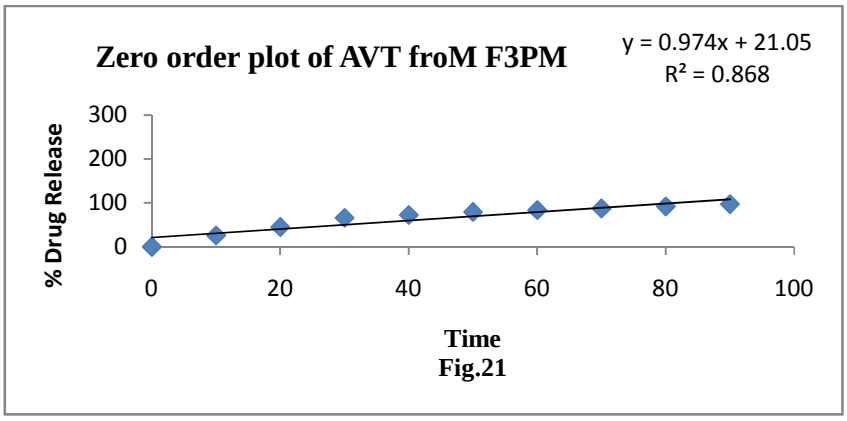


Fig.21

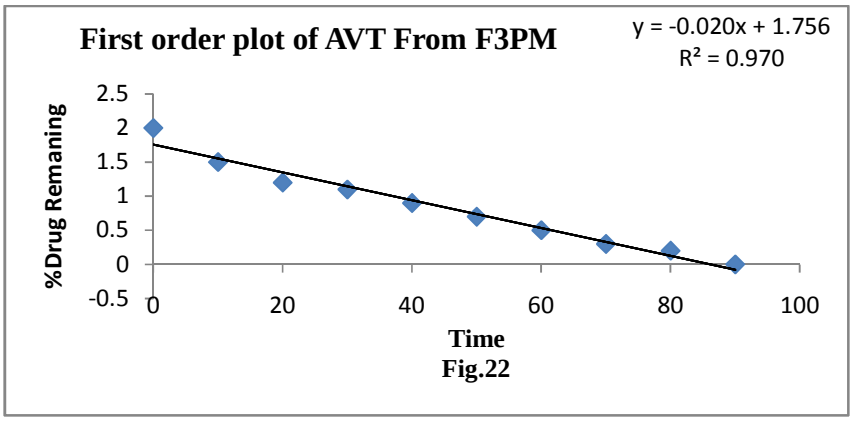


Fig.22

Table. 14 **In-vitro dissolution profile for F1SD**

Atorvastatin calcium					**Losartan Potassium**			
Time (min)	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**
0	0	0	0	0	0	0	0	0
10	24.16	24.38	23.65	24.06±0.374	78.75	79.17	79.05	78.99±0.216
20	42.91	44.05	43.35	43.43±0.574	81.36	80.85	81.18	81.13±0.258
30	63.17	63.41	62.75	63.11±0.334	86.66	87.14	87.25	87.01±0.313
40	71.41	70.78	71.36	71.18±0.350	89.88	89.72	90.11	89.90±0.196
50	80.98	82.02	81.57	81.52±0.521	93.15	92.62	92.75	92.84±0.276
60	89.12	88.73	89.25	89.03±0.270	94.35	94.17	93.94	94.15±0.205
70	92.26	92.44	91.72	92.14±0.374	94.91	95.15	95.22	95.09±0.162
80	94.63	95.29	95.35	95.09±0.399	96.13	96.28	95.85	96.08±0.218
90	96.22	95.66	96.18	96.02±0.312	97.18	96.94	97.32	97.14±0.192

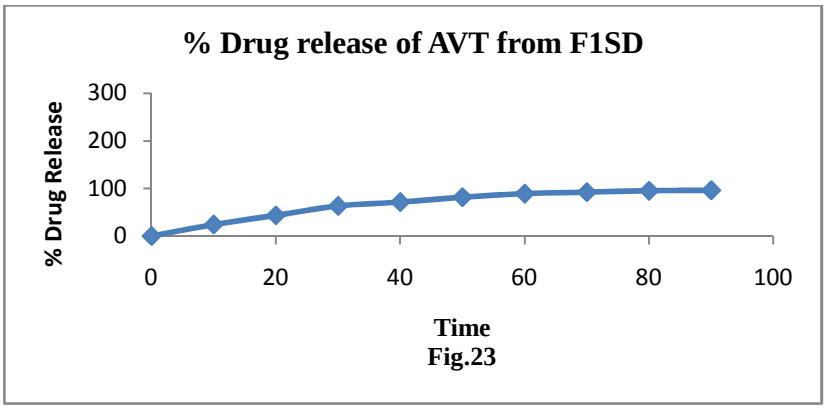


Fig.23

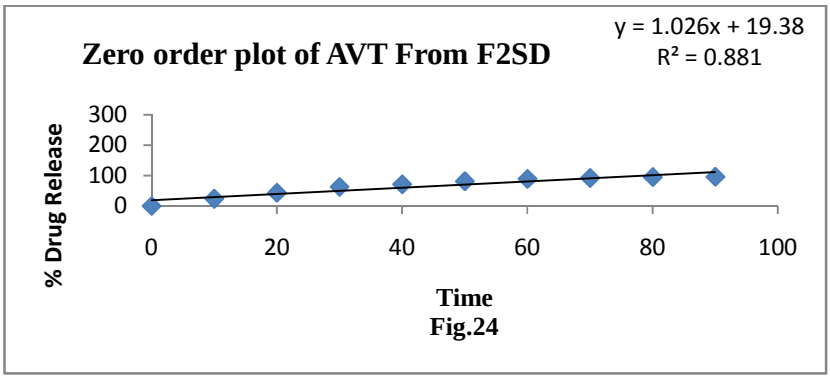


Fig.24

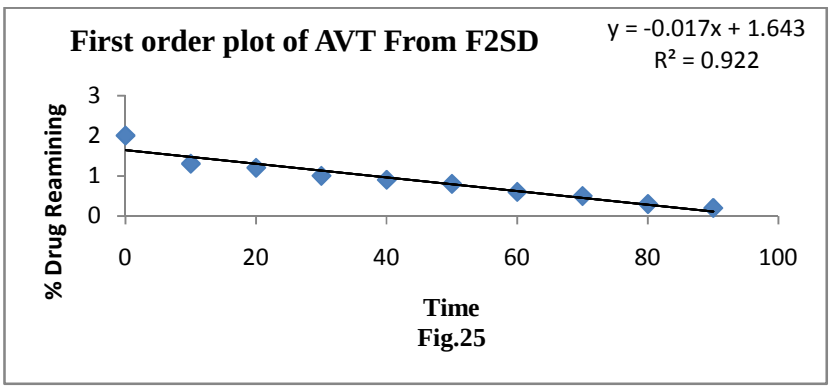


Fig.25

Table. 15 **In-vitro dissolution profile for F2SD**

Atorvastatin calcium					**Losartan Potassium**			
Time (min)	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**
0	0	0	0	0	0	0	0	0
10	18.78	19.25	19.43	19.15±0.335	80.33	79.90	80.11	80.11±0.215
20	36.55	35.98	37.08	36.53±0.550	83.72	84.25	84.06	84.01±0.268
30	74.33	74.09	73.85	74.07±0.240	88.28	88.16	87.92	88.12±0.183
40	79.81	80.45	80.36	80.20±0.346	90.76	91.04	91.18	90.99±0.213
50	86.22	86.05	85.78	86.01±0.221	93.10	93.24	93.43	93.25±0.165
60	88.17	87.93	88.15	88.08±0.133	95.88	96.05	96.16	96.03±0.1411
70	90.25	90.44	90.36	90.35±0.095	97.09	97.17	96.95	97.07±0.111
80	94.41	93.75	94.17	94.11±0.334	97.14	97.05	97.32	97.17±0.135
90	96.72	96.98	97.24	96.98±0.260	98.18	98.35	98.54	98.35±0.1801

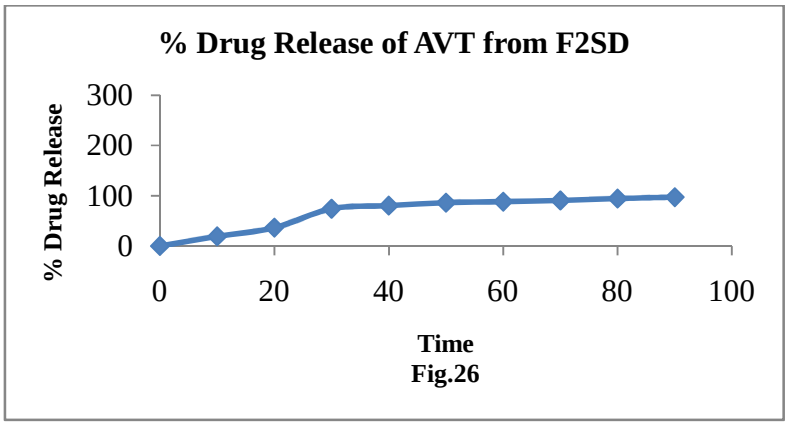


Fig.26

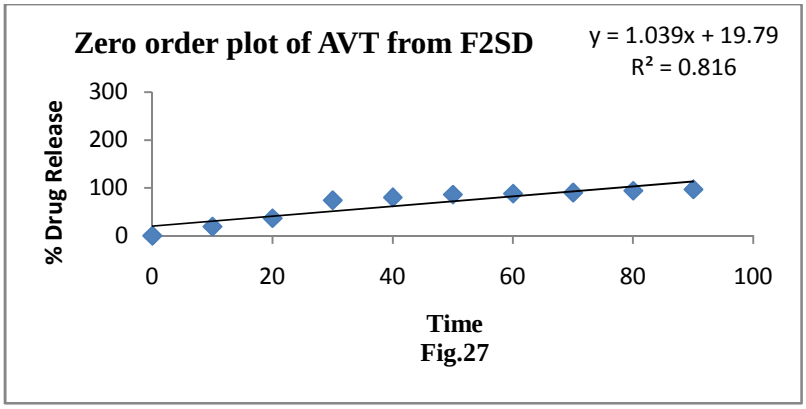


Fig.27

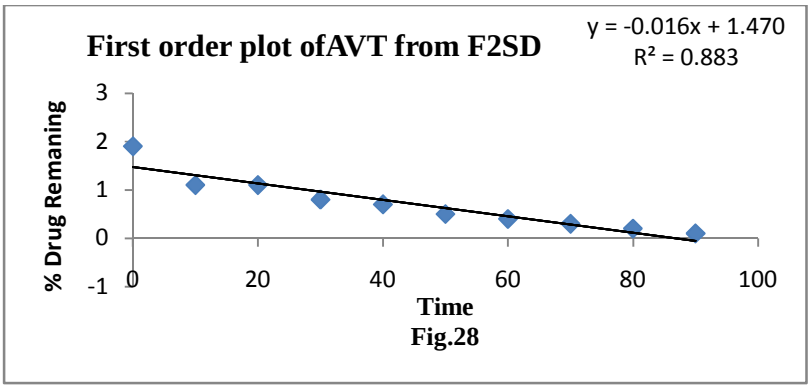


Fig.28

Table. 16 **In-vitro dissolution profile for F3SD**

Atorvastatin calcium					**Losartan Potassium**			
Time (min)	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**	**Trail 1**	**Trail 2**	**Trail 3**	**Mean ± SD**
0	0	0	0	0	0	0	0	0
10	30.77	30.82	31.14	30.91±0.200	84.96	85.55	86.02	85.57±0.531
20	56.96	57.05	57.12	57.04±0.080	89.14	88.77	89.22	89.04±0.240
30	71.08	71.32	70.80	71.06±0.260	91.85	92.08	92.16	92.03±0.160
40	80.78	80.93	81.23	80.98±0.229	95.11	95.20	94.90	95.07±0.153
50	89.80	89.71	90.16	89.89±0.238	96.06	96.31	96.23	96.02±0.127
60	92.85	93.03	93.10	92.79±0.129	96.89	97.17	97.40	97.15±0.255
70	96.30	95.79	96.13	96.07±0.259	98.15	98.11	97.95	97.76±0.105
80	97.55	97.22	97.40	97.39±0.165	98.12	98.10	98.33	98.18±0.127
90	98.14	98.10	97.87	98.03±0.145	98.87	99.02	99.20	99.03±0.165

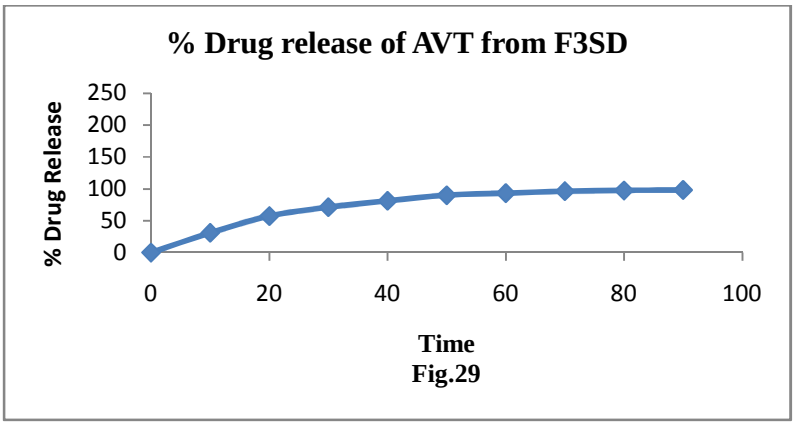


Fig.29

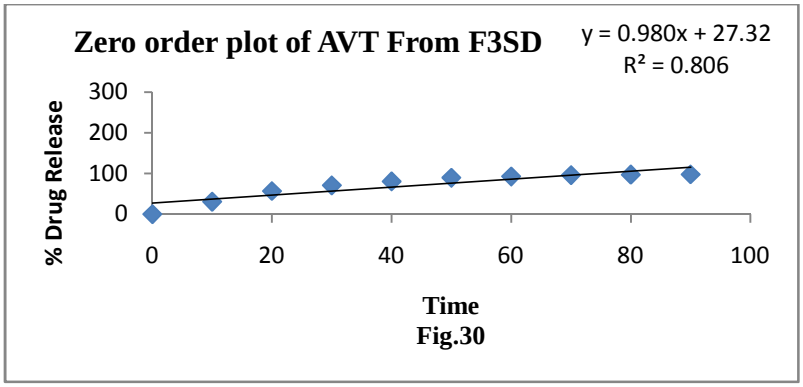


Fig.30

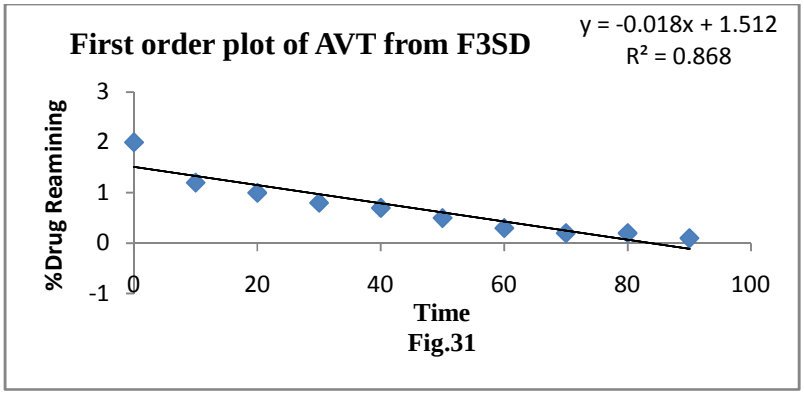


Fig.31

Table. 17 **Release kinetic study**

Formulation Code	AVT	LSP	PHYSICAL MIXTURE			SOLID DISPERSION		
			F1PM	F2PM	F3PM	F1SD	F2SD	F3SD
Zero order "R^2"value	0.989	0.992	0.894	0.884	0.868	0.881	0.816	0.806
First order "R^2"value	0.994	0.997	0.946	0.959	0.970	0.922	0.883	0.868
Best fit model	First order	First order	First order	First order	First order	First order	First order	First order

Table. 18 **Comparative % Dissolution of physical mixtures**

Time (mins)	F1PM		F2PM		F3PM	
	AVT	LSP	AVT	LSP	AVT	LSP
0	0	0	0	0	0	0
10	21.05	79.93	18.82	79.21	25.92	80.92
20	41.12	82.36	36.14	83.46	45.06	85.88
30	61.05	84.12	64.11	87.05	66.01	89.09
40	69.01	86.12	70.01	91.11	72.58	92.77
50	75.14	89.54	78.20	92.61	79.36	94.08
60	80.12	91.29	83.02	94.08	83.57	95.73
70	87.30	91.87	87.11	95.23	87.33	97.53
80	91.08	94.16	92.52	96.19	92.14	97.73
90	94.26	95.91	95.05	97.04	97.05	98.28

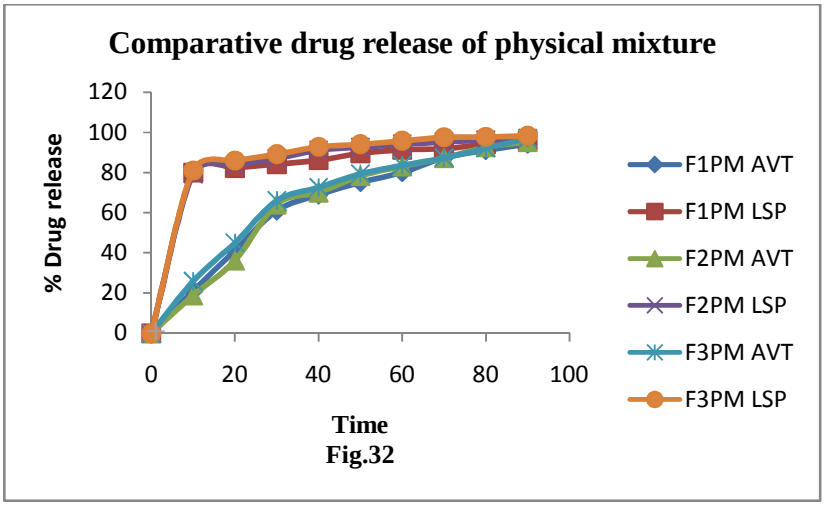


Fig.32

Table. 19 **Comparative % dissolution profile of solid dispersions**

Time (mins)	F1SD		F2SD		F3SD	
	AVT	LSP	AVT	LSP	AVT	LSP
0	0	0	0	0	0	0
10	24.06	78.99	19.15	80.11	30.91	85.57
20	43.43	81.13	36.53	84.01	57.04	89.04
30	63.11	87.01	74.09	88.12	71.06	92.03
40	71.18	89.90	80.20	90.99	80.98	95.07
50	81.52	92.84	86.01	93.25	89.89	96.02
60	89.03	94.15	88.08	96.03	92.99	97.15
70	92.14	95.09	90.35	97.07	96.07	97.76
80	95.09	96.08	94.11	97.17	97.39	98.18
90	96.02	97.14	96.98	98.35	98.03	99.03

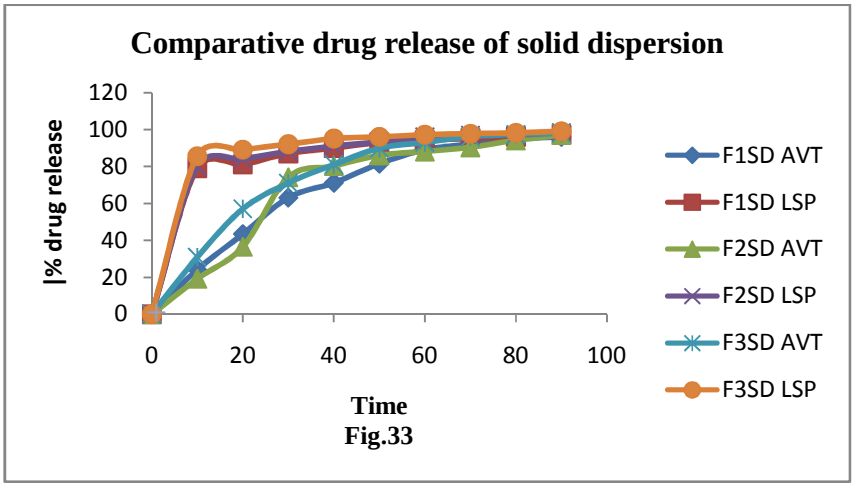


Fig.33

DISCUSSION

9. DISCUSSION

The results of the present study demonstrate that a novel drug-drug solid dispersion approach can improve dissolution and pharmacokinetic characteristics of the poorly soluble drug that was presented with the soluble drug. This novel approach will obviate the need for inclusion of physiological water soluble inert carriers in solid dispersion and so cost effective. Besides, this approach stabilizes the formulation from the effect of moisture that is normally encountered in solid dispersions prepared with physiological inert carriers.

In the present study AVT-LSP, used in the treatment of hypertension was selected as a model for this novel drug – drug solid dispersion approach and its physiochemical, *in vitro* release were investigated. AVT though rapidly absorbed from the GIT following oral administration, its poor solubility may pose dissolution rate limited absorption problem. The *in vitro* release of solid dispersion has shown enhanced dissolution of AVT as compared to physical mixture or solid dispersion.

The amorphous form of AVT was more soluble than its crystalline form and so an improved dissolution of AVT was observed from solid dispersion. Additionally LSP which is freely soluble has increased the solubility of AVT due to its solvent effect as shown in phase solubility study.

The pure drug AVT at 90 min dissolved 59% of release and pure drug LSP AT 90 min dissolved 98% of release. The PM AVT shows at 90 min dissolved 97% of release the PM LST shows at 90min dissolved 98% of release. The SD AVT shows at 90min dissolved 98% of release the SD LSP shows at 90min dissolved 99% of release.

The dissolution of AVT was better from AVT-LSP solid dispersion as compared to PM and pure drug.

CONCLUSION

10. CONCLUSION

- The present study shows improved dissolution of AVT from a modified novel drug - drug solid dispersion along with LSP.
- Dissolution of AVT was better from AVT - LSP solid dispersion as compared to physical mixture and pure drug.
- This novel solid dispersion is stable as no physiological inert carriers that are affected by moisture are used.
- Cost effective and economical as this approach is free of the economical burden of physiological inert carriers.

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